CLAIMS

1. A medical agent comprising a reagent conjugated to an anti-lymphoma antibody or a variant thereof, wherein the reagent is a single molecule with at least three functional parts b) - d), wherein

a) a trifunctional cross-linking moiety is coupled to

b) an affinity ligand via a linker 1, to

c) an effector agent via a covalent bond, optionally via a linker 2, and to

d) a biomolecule reactive moiety, optionally via a linker 3, wherein said biomolecule reactive moiety is an anti-lymphoma antibody reactive moiety being capable of forming a bond with the anti-lymphoma antibody or a variant thereof, thereby forming the conjugate, and wherein the anti-lymphoma antibody or variant thereof is interacting with one or more different CD antigens present on the surface of lymphoma tumour cells.

2. The medical agent according to claim 1, wherein the anti-lymphoma antibody or variant thereof is monoclonal and is interacting with one or more CD antigen(s) chosen from the group of CD1 to CD247.

3. The medical agent according to claim 2, wherein the anti-lymphoma antibody or variant thereof is interacting with CD19, CD20, CD22, and CD30, most preferably CD20.

4. The medical agent according to any one of the preceding claims, wherein the anti-lymphoma antibody is ibritumomab, rituximab, or tositumomab, preferably rituximab.

5. The medical agent according to any one of the preceding claims, wherein the anti-lymphoma antibody variant has the same or essentially the same ability as the anti-lymphoma antibody to bind to both the anti-lymphoma antibody reacting moiety and said CD antigen/-

antigens on the surface of lymphoma tumour cells, and wherein said variant is an antibody derivative, preferably the $F(ab')_2$, $F(ab')$, or $F(ab)$ fragment; genetically engineered hybrids or chemically synthesized peptides, preferably chimeric or humanized antibodies, and single chain antibodies.

6. The medical agent according to any one of the preceding claims, wherein the anti-lymphoma antibody or variant thereof binds to said cell surface antigen(s) on lymphoma tumour cells with an affinity binding constant of at least $5x10^6M^{-1}$, preferably at least 10^8M^{-1}.

7. The medical agent according to any one of the preceding claims, wherein the bond formed between the anti-lymphoma antibody reactive moiety and the anti-lymphoma antibody or a variant thereof is either covalent or non-covalent with a binding affinity constant of at least 10^8M^{-1}.

8. The medical agent according to claim 1, wherein the anti-lymphoma antibody reactive moiety is chosen from a group of active esters consisting of N-hydroxysuccinimide esters, sulfo-N-hydroxysuccinimide esters, and phenolic esters; aryl and alkyl imidates; alkyl or aryl isocyanates or isothiocyanates reacting with amino groups on the anti-lymphoma antibody, or maleimides or alpha-haloamides reacting with sulfhydryl groups on the anti-lymphoma antibody; or aryl or alkylhydrazines or alkyl or arylhydroxylamines reacting with aldehyde or ketone groups naturally occurring or synthetically produced on the anti-lymphoma antibody.

9. The medical agent according to claim 8, wherein said anti-lymphoma antibody reactive moiety also includes variants having essentially the same ability to bind to said anti-lymphoma antibody.

10. The medical agent according to claim 1, wherein the effector agent is a radionuclide binding moiety, optionally provided with a radionuclide, a synthetic or naturally occurring toxin, an enzyme capable of convert-

ing pro-drugs to active drugs, immunosuppressive or immunostimulating agents, radiosensitizers, enhancers for X-ray or MRI or ultrasound, non-radioactive elements, which can be converted to radio active elements by means of external irradiation after that anti-lymphoma antibody carrying said element has been accumulated to specific cells or tissues, or photoactive compounds or compounds used in photo imaging or photo dynamic therapy, or any other molecule having the same or similar effect, directly or indirectly, on lymphoma cells or lymphoma tissues.

11. The medical agent according to claim 10, wherein the effector agent comprises aryl halides and vinyl halides for radionuclides of halogens, N_2S_2 and N_3S chelates for Tc and Re radionuclides, amino-carboxy derivatives, preferably EDTA and DTPA or derivatives thereof, and cyclic amines, preferably NOTA, DOTA and TETA, and derivatives thereof, for In, Y, Pb, Bi, Cu, Sm and Lu radionuclides, or any other radionuclide capable of forming a complex with said chelates.

12. The medical agent according to claim 11, wherein the DTPA derivatives are Me-DTPA, CITC-DTPA, and cyclohexyl-DTPA.

13. The medical agent according to any one of claims 10-12, wherein the effector agent comprises DOTA and is provided with Y-90 for therapeutic application or In-111 for diagnostic application.

14. The medical agent according to any one of claims 10-13, wherein the effector agent is provided with positron imaging radionuclides, preferably F-18, Br-75, Br-76, and I-124; therapeutic radionuclides, preferably Y-90, I-131, In-114m, Re-186, Re-188, Cu-67, Sm-157, Lu-177, Bi-212, Bi-213, At-211, Ra-223; gamma imaging radionuclides, preferably Tc-99m, In-111, I-123, and I-125; beta radiation emitters, preferably scandium-46, scandium-47, scandium-48, copper-67, gallium-72, gallium-73, yttrium-90, ruthenium-97, palladium-100, rhodium-101,

palladium-109, samarium-153, lutetium-177, rhenium-186, rhenium-188, rhenium-189, gold-198, radium-212 and lead-212, gamma emitters, preferably iodine-131 and indium-m114; and positron emitters, preferably gallium-68 and zirconium-89.

15. The medical agent according to claim 1, wherein the affinity ligand is capable of binding to another molecule having affinity for said ligand with an affinity binding constant of at least 10^6M^{-1}, preferably at least 10^8M^{-1}.

16. The medical agent according to claim 15, wherein the affinity ligand is a moiety which binds specifically to avidin, streptavidin or any other derivatives, mutants or fragments of avidin or streptavidin having essentially the same binding function to this affinity ligand.

17. The medical agent according to claim 16, wherein the affinity ligand is biotin, or a biotin derivative having essentially the same binding function to avidin or streptavidin as biotin.

18. The medical agent according to claim 17, wherein the biotin derivative is chosen from the group consisting of norbiotin, homobiotin, oxybiotin, iminobiotin, desti-biotin, diaminobiotin, biotin sulfoxide, and biotin sulfone, or derivatives thereof having essentially the same binding function.

19. The medical agent according to any one of claims 15-18, wherein the stability against enzymatic cleavage, preferably against cleavage by biotinidase, of the bio-tinamide bond to release biotin has been improved by using biotin derivatives, preferably norbiotin or homo-biotin.

20. The medical agent according to claim 1, wherein the trifunctional cross-linking moiety is chosen from the group consisting of triaminobenzene, tricarboxybenzene, dicarboxyanyline and diaminobenzoic acid.

21. The medical agent according to claim 1, wherein linker 1 serves as an attaching moiety and a spacer between the trifunctional cross-linking moiety and the affinity ligand, preferably a biotin moiety, such that binding with avidin or streptavidin, or any other biotin binding species, is not diminished by steric hindrance.

22. The medical agent according to claim 21, wherein linker 1 contains hydrogen bonding atoms, preferably ethers or tioethers, or ionisable groups, preferably carboxylate, sulfonates, or ammonium groups to aid in water solubilisation of the biotin moiety.

23. The medical agent according to claim 22, wherein stability against enzymatic cleavage, preferably against cleavage by biotinidase, of the biotin amide bond to release biotin has been provided by introducing an alpha carboxylate or an N-metyl group in linker 1.

24. The medical agent according to claim 1, wherein linker 2 provides a spacer length of 1-25 atoms, preferably a length of 6-18 atoms.

25. The medical agent according to claim 24, wherein linker 2 contains hydrogen bonding atoms, preferably ethers or tioethers, or ionisable groups, to aid in water solubilisation.

26. The medical agent according to claim 1, wherein linker 2 is excluded.

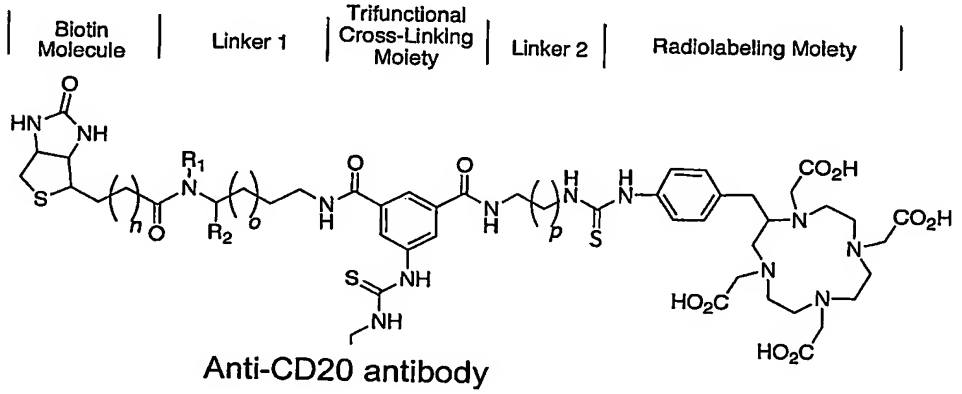
27. The medical agent according to claim 1, wherein linker 3 provides a spacer of a length of 1-25 atoms, preferably a length of 6-18 atoms.

28. The medical agent according to claim 27, wherein linker 3 contains hydrogen bonding atoms such as ethers or tioethers, or ionisable groups, preferably carboxylate, sulfonates, or ammonium groups to aid in water solubilisation.

29. The medical agent according to claim 1, wherein linker 3 is excluded.

30. The medical agent according to any one of the preceding claims, wherein more than one affinity ligand and/or more than one effector agent are bound to a trifunctional or tetrafunctional cross-linking moiety.

31. The medical agent according to any one of claims 1-25 and 27-28, wherein it is



bound to the effector agent,

wherein the anti-CD20 antibody preferably is rituximab, wherein n is 2-4, preferably 3; o is 1-6, preferably 3; p is 1-6, preferably 3; R_2 is $=CH_2OH$ or $-CO_2H$; and R_1 is $-CH_3$, $-CH_2OH$, or $-H$.

32. The medical agent according to any one of the preceding claims, wherein it is 3-(13'-thioureabenzyl-(DOTA)trioxadiamine-1-(13''-biotin-Asp-OH)trioxamine-5-isothio-cyanato-aminoisophthalate-ibritomumab, 3-(13'-thioureabenzyl(DOTA)trioxadiamine-1-(13''-biotin-Asp-OH)trioxamine-5-isothio-cyanato-aminoisophthalate-rituximab, or 1-Isocyanato-3-((1S'-(N-Biotinyl)-β-L-Asparty1)-4',7',10'-Trioxa-penta-Decanylamino)-1-((13-(Benzylthiourea-CHX-A'')-4,7,10-Trioxatridecanediamine)-Aminosiophthalate-rituximab, preferably 3-(13'-thioureabenzyl(DOTA)trioxadiamine-1-(13''-biotin-Asp-OH)trioxamine-5-isothio-cyanato-aminoisophthalate-rituximab.

33. A composition containing a medical agent according to any one of the preceding claims, wherein it further comprises physiologically acceptable additives, preferably an ammonium acetate solution.

34. A kit for extracorporeal elimination or at least reduction of the concentration of a non-tissue-bound therapeutic or diagnostic medical agent as defined in any one of claims 1-32 in the plasma or whole blood of a mammalian host, wherein said medical agent previously has been introduced into a mammalian host and kept therein for a certain time in order to be concentrated to the specific tissues or cells by being attached thereto, said kit comprising

a) the medical agent, and

b) an extracorporeal device comprising an immobilised receptor to which the affinity ligand adheres.

35. Use of a medical agent according to any one of claims 1-32 for the production of a medicament for the treatment of lymphoma, preferably non-Hodgkin's lymphoma.

36. A method for treatment of lymphoma, preferably non-Hodgkin's lymphoma, wherein anti-lymphoma antibodies or variants thereof as defined in any one of claims 2-6 are administered to a patient with a need thereof, wherein complexes formed between said anti-lymphoma antibodies or variants thereof and leukocytes having said one or more cell surface antigen(s) are then eliminated from the body of the patient, followed by administration of the medical agent according to any one of claims 1-32, optionally together with said anti-lymphoma antibodies or variants thereof as such, followed by extracorporeal elimination of the medical agent which has not been bound to the cell surface antigens on the lymphoma tumour cells.

37. The method according to claim 36, wherein the effector agent of the medical agent is ^{90}Y and the medical agent is administered in a single dose of more than 20 MBq/kg body weight.

38. The method for diagnosing lymphoma, preferably non-Hodgkin's lymphoma, wherein anti-lymphoma antibodies or variants thereof as defined in any one of claims 2-6 are administered to a patient with a need thereof, wherein complexes formed between said anti-lymphoma antibodies or variants thereof and leukocytes having said one or more cell surface antigen(s) are then eliminated from the body of the patient, followed by administration of the medical agent according to any one of claims 1-32, optionally together with said anti-lymphoma antibodies or variants thereof as such, followed by extracorporeal elimination of the medical agent which has not been bound to the cell surface antigens on the lymphoma tumour cells.

39. The method according to claim 38, wherein the effector agent of the medical agent is ^{90}Y or ^{111}In and the medical agent is administered in a dose range of 10-20, preferably 11-15, MBq/kg body weight in view of ^{90}Y and in a dose range of 20-250, preferably 50-150, MBq/kg body weight in view of ^{111}In.

40. A method for combined diagnosing and treatment of lymphoma, preferably non-Hodgkin's lymphoma, wherein a medical agent according to any one of claims 1-32, wherein the effector agent is ^{111}In, is administered to a patient in a dose range of 50-150 MBq/kg body weight, and a medical agent according to any one of claims 1-32, wherein the effector agent is ^{90}Y, is administered to the patient in a dose of more than 20 MBq/kg body weight, either in sequence at intervals of 6-8 days or simultaneously.

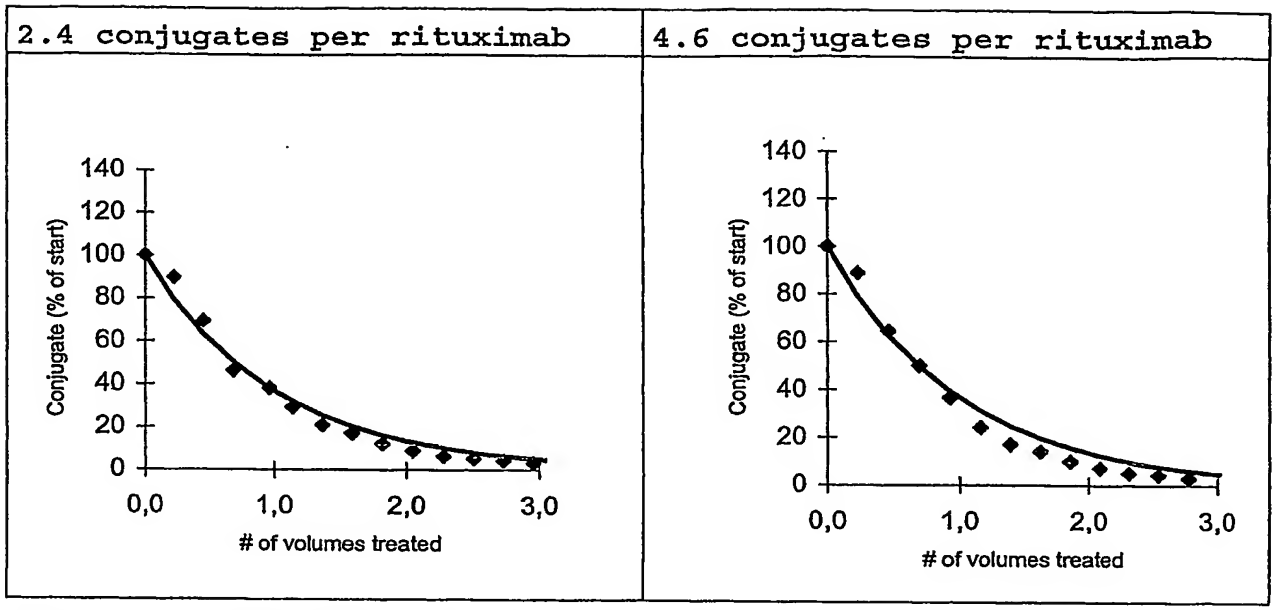
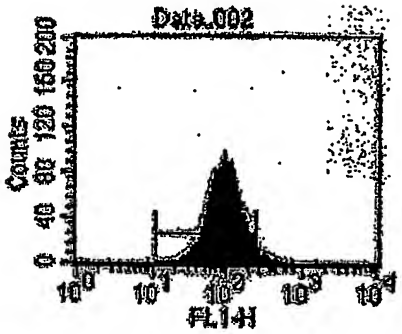
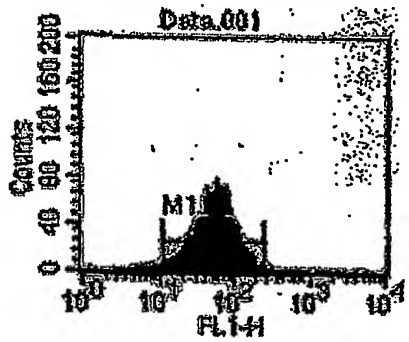


Figure 1: Depletion of 1033-rituximab conjugates during re-circulation through a miniaturised Mitradep®. The lines display the theoretically maximal possible depletion rate. As seen the depletion of 1033-rituximab is not different from the theoretical depletion line, i.e. all 1033-rituximab present in the solution passing through the device is removed.

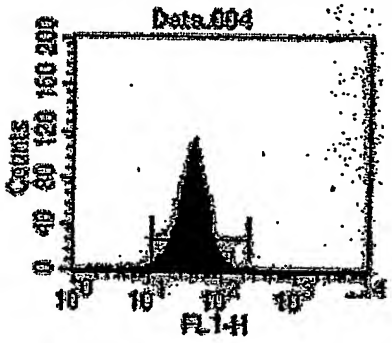
Biotin-Rituximab



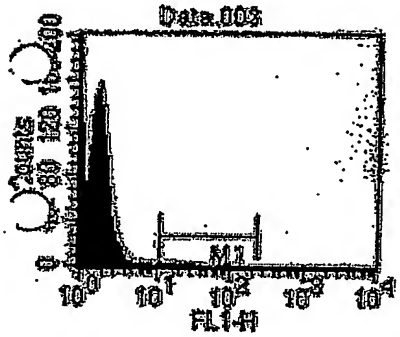
Biotin-mouse anti-CD20



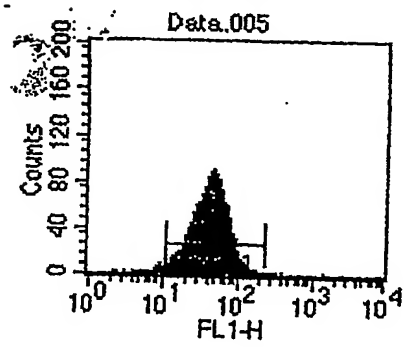
2.4 conjugate/Rituximab



Biotin-IgG



4.6 conjugate/Rituximab



PBS buffer

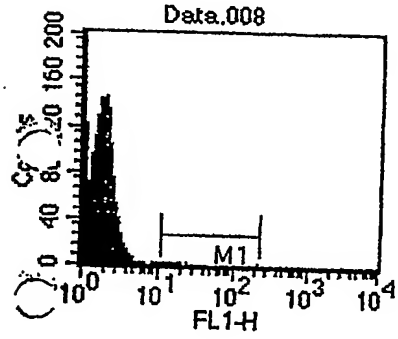


Figure 2: Flow cytometric assay of binding to the CD20-positive cell line

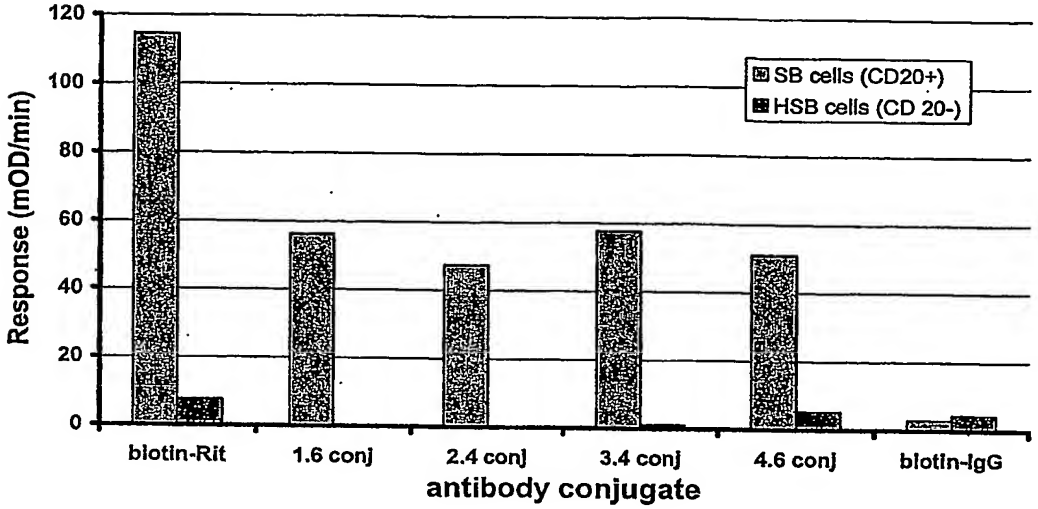


Figure 3: Binding of 1033-conjugates to a CD20+ (SB) and a CD20- (HSB) cell line. The binding is detected with an enzyme-labelled streptavidin.

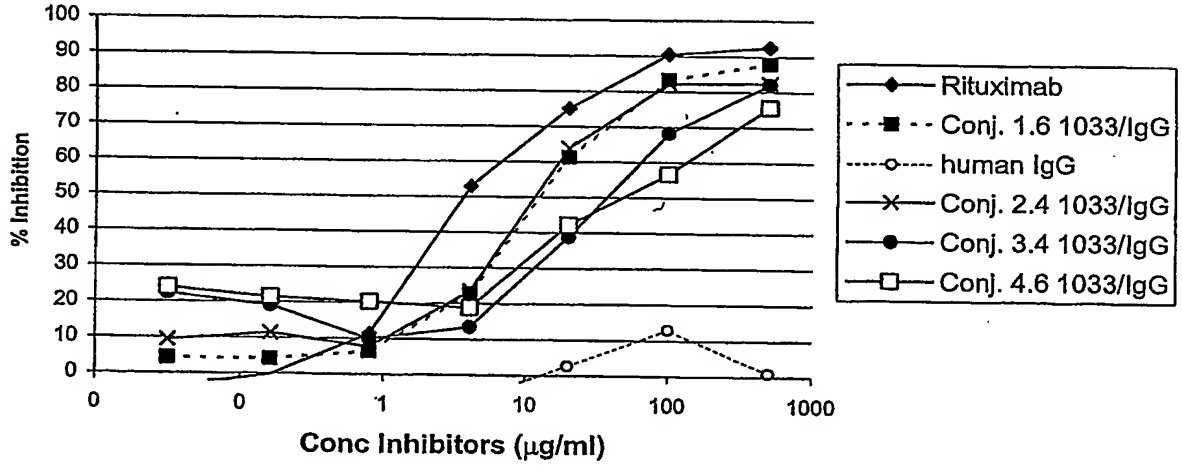


Figure 4: Competitive inhibition of ^{125}I-labelled rituximab binding to SB cells by cold rituximab and 1033-rituximab conjugates.

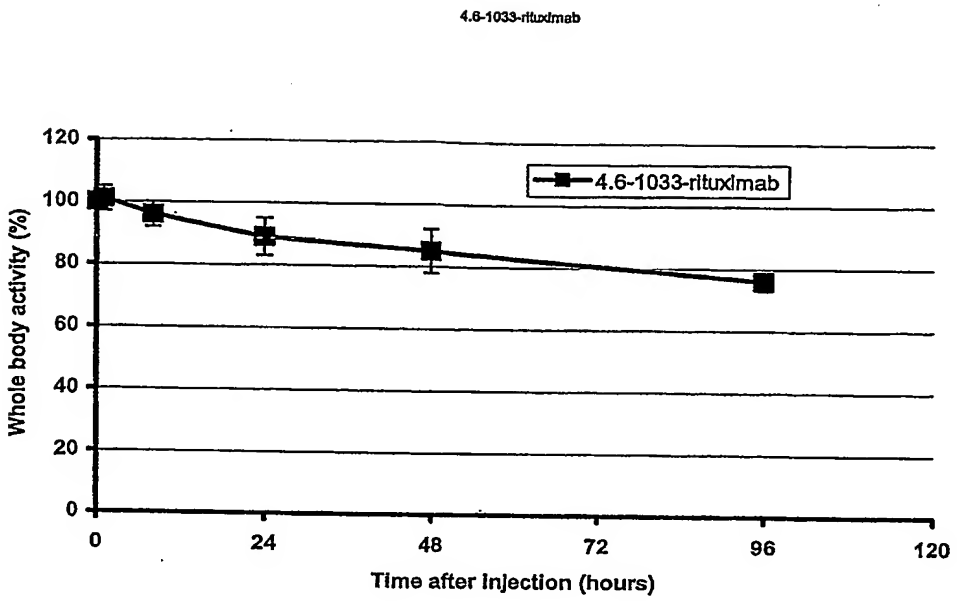


Figure 5: Whole body clearance of radioactivity in rats injected with ^{111}In-1033-rituximab antibody conjugates expressed as percentage ± std.dev. The data are corrected for radioactivity decay and background.

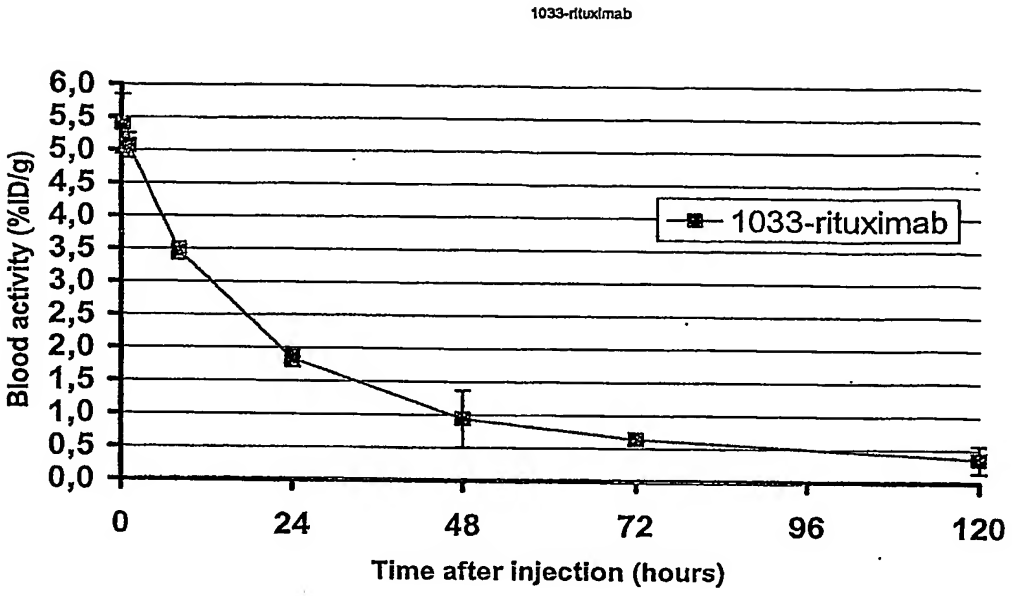


Figure 6: Blood clearance of ^{111}In-1033-rituximab antibody conjugates expressed as % injected dose/gram ± std.dev. The data are corrected for radioactivity decay.

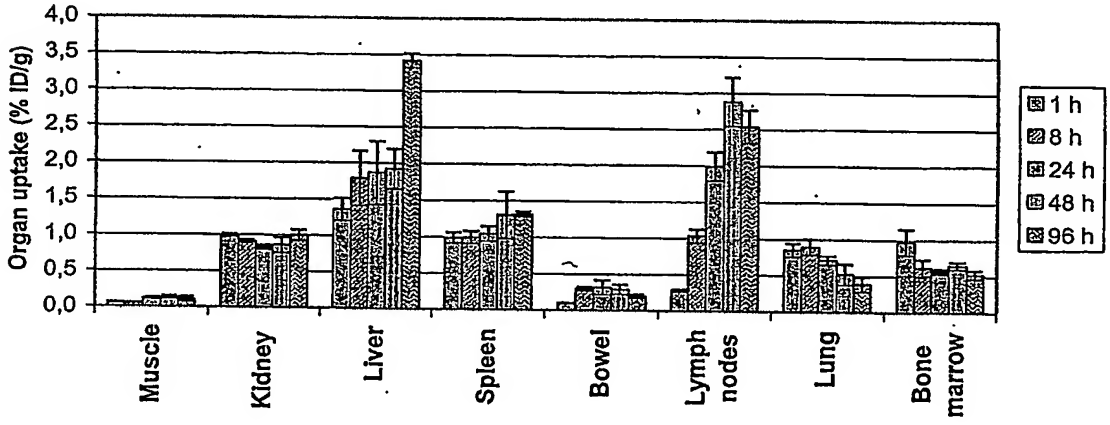


Figure 7: Biodistribution of ^{111}In-1033-rituximab (4.6 1033/IgG) in rats. The biodistribution is expressed as per cent of injected dose per gram tissue ± std.dev. The results are corrected for radiochemical decay.

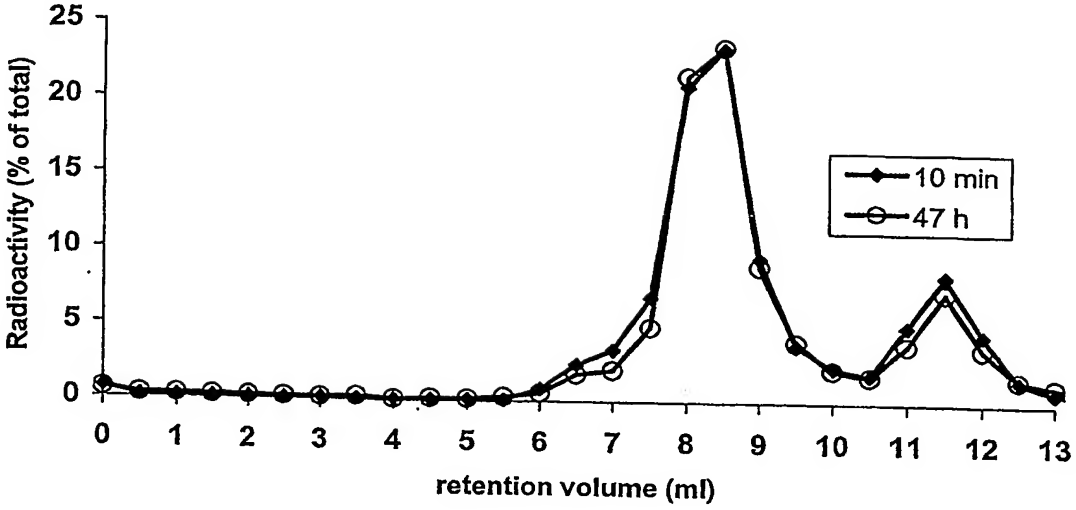


Figure 8: HPLC size exclusion separation of blood samples drawn from a rat injected with ^{111}In-1033-rituximab (4.6 1033/IgG).